

20. The method according to claim 19, wherein the chromatography is hydrophobic interaction.

## II. IN THE CLAIMS (MARKED SHEET)

Please cancel Claim 2, without prejudice or disclaimer. Such cancellation is not for any reason related to patentability under 35 USC §§101, 102, 103, and/or 112. No estoppel should result from said cancellation.

Please amend the claims as follows:

1. (Amended) A method of preparing naturally occurring Troponin I, which method comprises protecting free sulfhydryl groups of Troponin I under reducing conditions.
3. (Twice Amended) The method according to claim 1 [2], wherein sulfitylation comprises reacting [oxidized recombinant] Troponin I with sodium sulfite.
4. (Amended) The method according to claim 1, wherein the [recombinant] Troponin I is expressed in a bacterial expression system.
6. (Amended) The method according to claim 1, which further comprises purifying the sulfhydryl group [-]protected [recombinant] Troponin I.
13. (Amended) A method of purifying naturally occurring Troponin I, which method comprises subjecting Troponin I comprising sulfhydryl protecting groups to chromatography to purify the sulfhydryl group protected Troponin I

15. (Twice Amended) The method according to claim 14, wherein sulfitolysis comprises reacting [oxidized], denatured [recombinant] Troponin I with sodium sulfite

**IV. In the Specification (Marked Version)**

On page 8, line 3, please replace "tetrathionate" with - sulfite --.

**V. REMARKS****A. Specification Objections**

Typographical errors and minor amendments have been made to comply with the Examiner's objections to the specification. Such corrections do not create estoppel and were not made for any reason related to patentability under 35 USC §§ 101, 102, 103, and/or 112.

**C. 35 USC §112, 1<sup>st</sup> ¶**

Claims 1-9 and 13-20 stand rejected under 35 USC §112, 1<sup>st</sup> ¶, because the Examiner contends that the specification, while being enabling for sulfitolyzing and separating naturally occurring Troponin I (TnI) polypeptide, does not reasonably provide enablement for recombinant (mutant) TnI polypeptide. In an effort to further the prosecution of the case, Applicants have amended the claims to naturally occurring Troponin I. Such amendment is not a forfeit of the right to pursue the cancelled subject matter in a continuing application. Applicants believe the claims are in a condition for allowance and respectfully request such action.

The Examiner admits that the '031 patent does not teach deprotecting sulfitolized thiol groups and purifying Tnl protein. The Examiner stated the the '031 patent was relevant to Claims 1-5, 9, 13-15, and 17-19. Applicants assert that the '031 patent does not teach any claim within Applicants' invention, after amendment.

The Examiner then asserts that the '685 patent teaches deprotecting sodium sulfite reacted thiol groups of a polypeptide in order to obtain an active form of polypeptide, the deprotection carried out under reducing conditions. The Examiner stated the '685 patent was relevant to Claim 9. Applicants assert that the '685 patent does not teach any claim within Applicants' invention, after amendment.

The following Table illustrates Applicants' Claims **before the instant amendment** and the prior art the Examiner stated was relevant thereto:

CLAIM	Reference(s) cited as relevant by Examiner
1	Fujita; the '031 patent; the '685 patent;
2	the '031 patent
3	the '031 patent
4	Fujita; the '031 patent
5	Fujita; the '031 patent
6	Fujita
7	Fujita
8	Fujita
9	the '031 patent; the '685 patent
13	the '031 patent
14	the '031 patent
15	the '031 patent
16	Fujita; the '521 patent
17	Fujita; the '031 patent
18	Fujita; the '031 patent
19	Fujita; the '031 patent
20	Fujita

This Table illustrates Applicants' Claims **after the instant amendment** and the prior art the Examiner stated was relevant, as compared to the amended claims:

**D. 35 USC §112, 2<sup>nd</sup> ¶**

Claims 1-9 and 13-20 stand rejected under 35 USC §112, 2<sup>nd</sup> ¶, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Examiner has stated that Claim 1 is rejected because it fails to state the steps of protection. Applicants respectfully request reconsideration in light of the argument and amendment. It is clear from the specification what protecting free sulfhydryl groups of Troponin I under reducing conditions means. However, to further the prosecution of the case, without prejudice or disclaimer, Applicants have amended the claims. The amendments should not create any estoppel and Applicants expressly reserve the right to pursue the cancelled subject matter in a divisional application.

The Examiner further rejected the specification based upon a typographical error on page 8, lines 1-3. Applicants have corrected this error and respectfully request reconsideration.

**E. 35 USC 102(b) Rejections**

Claims 1, 4-8, 13 and 17-18 stand rejected under 35 USC §102(b) as being anticipated by an article in the *Eur. J Biochem.* (1994) 225, 1195-1201, to Al-Hillawi et al. Applicants have incorporated the limitations of Claim 2 into Claim 1 and Claim 14 into Claim 13, without prejudice or disclaimer, thereby obviating the rejections. Accordingly, Applicants respectfully request reconsideration.

Claims 1, 6, and 8 are rejected under 35 USC §102(e) as being anticipated by US Pat. No. 6,156,521 to Buechler (hereinafter referred to as the '521 patent). Applicants have incorporated the limitations of Claim 2 into Claim 1. Therefore, Applicants respectfully request reconsideration of the rejection.

**F. 35 USC §103(A) REJECTION**

Claims 1-9 and 13-20 stand rejected under 35 USC §103(a) as being obvious over an article to Fujita-Bakert et al. (J. Biochem., (1993) 114, pp. 438-444) (hereinafter referred to as Fujita), taken with Lile et al, US Pat No. 5,606,031 (hereinafter referred to as the '031 patent), Chace et al, US Pat No. 4,421,685 (hereinafter referred to as the '685 patent), and the '521 patent. The Examiner expressly notes that the new ground of rejection is based upon Applicants' amendment adding sodium sulfite.

The Examiner asserts that Fujita teaches purification of *E. coli* expressed Troponin I, as applied to Claims 1, 4-5 and 17-18. The Examiner further asserts that Fujita teaches purification using Q-Sepharose and Phenyl Sepharose columns as applied to Claims 16, 19 and 20. However, the Examiner admits that Fujita does not teach sulfitolization of the thiol group, denaturing and refolding of a protein. Applicants add that Fujita does not teach any aspect of any of the claims of Applicants' invention, after amendment.

The Examiner then asserts that the '031 patent teaches a method for the production of biologically active protein, as applied to Claims 1-5, 9, 13-15, and 17-19.

CLAIM	Reference(s) cited as relevant by Examiner
1	the '031 patent
2	Cancelled
3	the '031 patent
4	the '031 patent
5	the '031 patent
6	Combination of Fujita and the '031 patent
7	Combination of Fujita and the '031 patent
8	Combination of Fujita and the '031 patent
9	the '031 patent
13	the '031 patent
14	Cancelled
15	the '031 patent
16	the '521 patent
17	the '031 patent
18	the '031 patent
19	the '031 patent
20	Combination of Fujita and the '031 patent

The instant amendment incorporated the limitations of Claim 2 into Claim 1 and the limitation of Claim 14 into Claim 13. Accordingly, by the Examiner's own statements, the above table represents the art relevant, but not anticipatory to each Claim. Support for this statement is found in the fact that there are no Section 102 rejections that are any longer relevant to the amended claims. Accordingly, the art cited by the Examiner is no longer relevant to the claims for the Section 103 rejection. The Examiner's contentions on the teaching of the art are no longer accurate.

It has long been the law that an obviousness determination requires an analysis of four factors. The factors are 1) scope and content of prior art; 2) the differences between the prior art and the claims at issue; 3) the level of ordinary skill in the art; and, 4) objective evidence of non-obviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966). Here, the Examiner did not consider these factors.

To ascertain the scope of the prior art, a court examines "the field of the inventor's endeavor," *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 620, 225 USPQ 634, 638 (Fed. Cir. 1985), and "the particular problem with which the inventor was involved," *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983) (*quoting In re Wood*, 599 F.2d 1032, 1036, 202 USPQ 171, 174 (CCPA 1979)), at the "time the invention was made," sec 35 U.S.C. Section 103(a). In support of his contention, the Examiner states that it would have been obvious to one of ordinary skill in the art to combine the teachings of the '031 patent and Fujita because the '031 patent teachings offer the advantage of bacterial produced mammalian protein.... The Examiner further asserts that because the prior art discloses how to protect cysteine residues of TnI from oxidation, that one of ordinary skill in the art would have considered protecting thiol groups of TnI during purification and deprotecting the modified thiol groups by removing sulfitolyzing moieties from protected thiol groups followed by the protein refolding.

In response, Applicants assert that the Examiner has cited four pieces of prior art to attempt to arrive at Applicant's invention. Then, after Applicants amendment, further combinations of the teachings of the prior art are required. There is no motivation to make these changes. A determination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. There must be a teaching or suggestion within the prior art to look to particular sources of information, to select particular elements, and to combine them in the way they were combined by the inventor. *See Heidelberg Druckmaschinen AG v. Hantscho Commercial Prods., Inc.*, 21 F.3d 1068, 1072, 30



USPQ2d 1377, 1379 (Fed. Cir. 1994) ("When the patented invention is made by combining known components to achieve a new system, the prior art must provide a suggestion or motivation to make such a combination."); *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 935, 15 USPQ2d 1321, 1324 (Fed. Cir. 1990) (the prior art must suggest to one of ordinary skill in the art the desirability of the claimed composition); *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985). Here, the Examiner has identified some motivation, but such motivation is very attenuated. Further, in light of Applicants' amendment, such motivation is even more attenuated and non-existent.

As stated in the previous Office Action Response, the law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. *See, e.g., C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998). Here, in light of Applicants' amendments, there is no motivation to combine the attenuated teachings.

Accordingly, in light of the amendments and the lack of any suggestion or motivation to combine these abstract pieces of prior art, Applicant respectfully requests reconsideration of the rejection.

#### **F. Double Patenting and Provisional-Type Double Patenting**

Applicant has abandoned the other application. Therefore, Applicant respectfully requests reconsideration of the rejection.

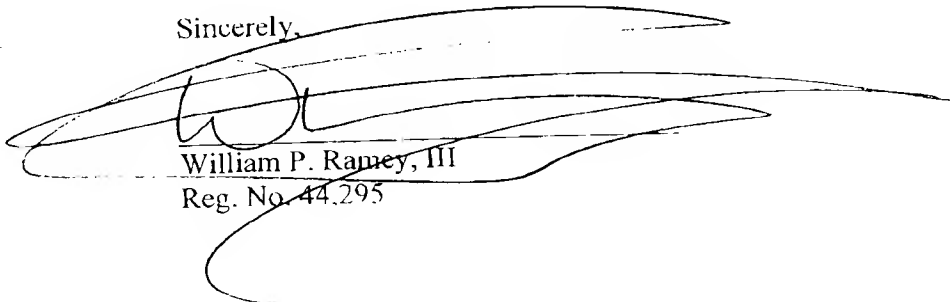
**VI. CONCLUSION**

The application is believed in a condition for allowance and Applicants respectfully request such action. Applicant respectfully requests an interview with the Examiner. Please call the below undersigned attorney at (302) 933-4034. Please charge deposit account number 02-2334 for any required fees and credit any credits.

Date:

4/2/03

Sincerely,



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